

REMARKS

Reconsideration and withdrawal of the objections to the specification and rejections of the claims, in view of the remarks and amendments herein, is respectfully requested. Claims 1, 21, 25, 27, 29-32, 43, 51, 53, and 55-59 are amended, claims 26 and 52 are canceled, and claims 63-64 are added. Claims 1-7, 9-25, 27, 29-46, 48-51, 53, 55-59, and 61-64 are now pending in this application.

The Examiner and Ms. Lee are thanked for the courtesies extended to Applicant's Representative in the telephonic interview conducted on June 10, 2007, in which the objections to the specification and rejections of the claims were discussed.

Figures 4, 6, 8, 9, 11, and 13 were objected to. The amendments to paragraphs beginning on page 19, line 26, page 20, lines 6, 13, 17, and 30, and page 21, line 18 of the specification address those objections.

The amendments to claims 1 and 21, to move the word "two" and delete "tannic acid", respectively, render moot the objections to those claims.

The 35 U.S.C. § 112, Second Paragraph, Rejections

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, and 61-62 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. In particular, the Examiner alleges that the omissions are the correlation between the identity and structural limitations of each composition/agent and the recited cellular effect achieved by that agent. The Examiner continues asserting that claims 1, 4, 43, 46, and 61 recite cellular functions achieved by one or more agents, but that the identity of the agent that performs the function is not recited, and claims 21 and 43 recite several agents, but that the function that each agent performs in the target cell is not recited. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

The amendments to claims 1, 21 and 43 address the § 112(2) rejection of those claims.

With respect to claims 4 and 46, which depend on claims 1 and 43, respectively, those claims recite "further comprising" contacting the cell with "an agent," i.e., the agent recited in claims 4 and 46 is a third agent. Claim 61, which depends on claim 1, recites that the second

agent enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome. The second agent recited in claim 1 inhibits proteosome proteolytic activity. Therefore, claims 4, 46 and 61 are clear.

Accordingly, withdrawal of the § 112(2) rejections respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, and 61-62 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

The Examiner asserts that 1) with respect to agents capable of altering the cellular uptake of rAAV, DOXIL® is the only species whose complete structure is disclosed to perform that function, and that no other identifying characteristics identify *a priori* an agent that would perform that function; 2) with respect to agents capable of modulating rAAV processing in the cell, LLnL, a proteosome inhibitor, is the only species whose complete structure is disclosed to perform that function, and that no other identifying characteristics identify *a priori* an agent that would perform the claimed function; 3) Applicant must explicitly point out in the specification support for other agents useful in the methods; 4) the functional characteristic(s) of each agent has not been coupled with a known or disclosed correlation between function and structure; and 5) the specification does not provide a sufficient description of a representative number of species by an actual reduction to practice.

To provide an adequate written description for a claimed genus, the specification can provide a sufficient description of a representative number of species by an actual reduction to practice, reduction to drawings or by a disclosure of relevant, identifying characteristics, i.e., by a structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112(1) Written Description Requirement, Fed. Reg., 66, 1099 (2001)).

It is disclosed that agents useful in the methods of the invention are those that individually have different or overlapping activities (page 9). It is also disclosed that doxorubicin is an agent that may facilitate viral binding to proteosomes and/or subsequent

transport into the nucleus (page 9), i.e., doxorubicin alters intracellular viral trafficking or processing, not cellular uptake of AAV as alleged by the Examiner. Further, LLnL and Z-LLL are disclosed as agents that more significantly inhibit core proteolytic activity of proteosomes (page 9).

With regard to proteosome inhibitors, chemotherapeutics, lipid lowering agents, antibiotics and tannic acid, those agents are known to the art. See, for instance, U.S. Patent No. 7,122,335, and the abstracts for Walsh et al. (Biochem. Soc. Trans., 31:487 (2003)), Phillips et al. (Curr. Op. Invest. Drugs, 3:1701 (2002)), Denny (Curr. Med. Chem., 9:1655 (2002)), Malhotra et al. (Cancer Biol. Ther., 2:52 (2003)), Backes et al. (Ann. Pharmacother., 39:523 (2005)), Davidson et al. (Prog. Cardiovasc. Dis., 47:73 (2004)), and Chung et al. (Crit. Rev. Food Sci. Nutr., 38:421 (1998)), a copy of each is enclosed herewith). Applicant need not teach what is well known to the art.

Other specific agents useful in the methods are disclosed at, for example, page 51, line 23-page 52, line 8 and page 86, lines 14-31 of the specification.

Thus, the claims recite relevant, identifying characteristics for the agents, i.e., each agent alone enhances intracellular rAAV transduction, and one agent is a chemotherapeutic, a lipid lowering agent, an antibiotic or a tannic acid, e.g., epoxomicin, doxorubicin, daunorubicin, idarubicin, epirubicin, aclarubicin, or simvastatin and the other agent inhibits proteosome proteolytic activity or enhances AAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome.

Therefore, the claims satisfy the written description requirement of § 112(1).

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, and 61-62 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Examiner asserts that the breadth of the claims is exceptionally large, encompassing an enormous genus of rAAV, an enormous genus of mammalian cells and a broad genus of distinctly different and mutually exclusive cell biological processes, and that the artisan would essentially have to experiment by trial and error each combinatorial permutation of compounds embraced by the claims and capable of performing the recited functions. The Examiner concludes that in view of the lack of guidance, working examples, breadth of the claims, the

level of skill in the art and state of the art at the time the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The Examiner also asserts that the claims embrace rAAV transduction *in vivo* and that the instant specification does not disclose formulations of the enormous genus of structurally undisclosed agents identified only by their functional activity in a cell, wherein the at least two agents from the enormous genus are used in an amount that together at least additively enhance rAAV transduction *in vitro*, *ex vivo* and in a patient, and that the specification does not clearly define and distinguish those "proteasome modulating agents" that do or do not inhibit proteasome proteolytic activity, and which art-recognized proteasome modulating agents are or are not to be used in the method.

It is Applicant's position that the preparation of rAAV is within the skill of the art and a large number of different rAAV have been prepared. Moreover, AAV has a broad host range (see Muzyczka, *Curr. Top. Microbiol. Immunol.*, 58:97 (1992); a copy is enclosed herewith), i.e., it is known to infect many types of cells. Further, the specification discloses the infection of HeLa cells, IB3 cells, A549 cells, ferret fibroblasts, mouse lung, trachea and bronchi, and airway epithelia with rAAV.

While agents useful in the methods of the invention may alter different or similar biological processes, such as processes recited in the dependent claims, those agents are chemotherapeutics, lipid lowering agents, antibiotics, tannic acid, or inhibitors of the proteolytic activity of proteasomes, or enhance rAAV transduction after viral binding to the cellular membrane and before second strand synthesis which yields an expressible form of the viral genome. As discussed above, chemotherapeutics, lipid lowering agents, antibiotics, tannic acid, and inhibitors of the proteolytic activity of proteasome are known. As also discussed above, the specification discloses particular agents at page 51, line 23-page 52, line 8 and page 86, lines 14-31 that may be employed in the methods of the invention. The specification also discloses working examples of agents that enhance rAAV transduction. In addition, it is Applicant's position that the level of skill in the art is high.

With regard to the alleged undue experimentation to identity combinations of agents that at least additively enhance rAAV transduction, the Examiner simply cannot reasonably contend

that a program to locate biomolecules with target biological or physical properties would not be carried out by the art because the results cannot be predicted in advance.

In fact, the Federal Circuit has explicitly recognized that the need, and methodologies required, to carry out extensive synthesis and screening programs to locate biomolecules with particular properties do not constitute undue experimentation. In re Wands, 8 U.S.P.Q.2d 1400, 1406-1407 (Fed. Cir. 1988), the Court stated:

The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

Likewise, practitioners in the art related to the present application would be well-equipped to prepare and/or screen combinations of agents falling within the scope of the claims to identify those agents that at least additively enhance AAV transduction. See also, Hybritech Inc. v. Monoclonal Antibodies Inc., 231 U.S.P.Q. 81, 84 (Fed. Cir. 1986) (evidence that screening methods used to identify characteristics [of monoclonal antibodies] were available to art convincing of enablement). Thus, the fact that a given claim may encompass a variety of agents, mammalian cells and rAAVs is not dispositive of the enablement issue, particularly in an art area in which the level of skill is very high and in which screening of large numbers of compounds has been standard practice for at least ten years (Ex parte Forman, 230 U.S.P.Q.2d 456 (Bd. App. 1986).

Evidence that screening numerous compounds to detect the effect of the compound on virus infection or replication is within the skill of the art is provided in the abstracts for Cheng et al. (Antimicro. Agents Chemother., 48:2437 (2004)) and Dhanak et al. (J. Biol. Chem., 277:38344 (2002)) (a copy of each is enclosed herewith).

With regard to the *in vivo* use of rAAV and the recited agents, the Examiner is requested to consider that rAAV has been employed *in vivo* (see the abstract for Wu et al. (Vision Res., 48:1648 (2008)), Chen et al. (Pathol. Oncol. Res., epub May 29, 2008)) and Hsu et al. (Pharm. Res., epub February 22, 2008)); a copy of each is enclosed herewith)), as have chemotherapeutics, lipid lowering agents, antibiotics and tannic acid (a food additive).

And with respect to "proteosome modulating agents," the claims do not recite that phrase, although the specification discloses that those agents do not include agents that inhibit the proteolytic activity of the proteosome.

The Examiner has again cited Kapturczak et al. (Curr. Mol. Med., 1:245 (2001)), Mah et al. (Molecular Ther., 6:106 (2001)), and Goncalves (Virology J., 2:43 (2005)) to support the contention that the delivery of AAV is unpredictable, but failed to respond to Applicant's argument in the Amendment filed on January 31, 2008 that these documents are not on point. Kapturczak et al. disclose that rAAV offers a vehicle for safe, long-term therapeutic gene transfer and note that substantial progress has been made in addressing AAV related issues, such as packaging capacity, packaging systems, and the availability of virus receptors on some cell types. For instance, to overcome subtherapeutic levels of transduction after systemic delivery, Mah et al. disclose modifying AAV2 virions with microspheres.

Moreover, while the process regulating AAV trafficking into the nucleus may not be fully understood (Goncalves), the specification discloses that agents that modulate that process may be useful in the claimed methods.

However, none of Kapturczak et al., Mah et al. or Goncalves relate to the use of exogenously administered agents to enhance AAV transduction and so do not evidence the level of (or lack of) predictability in the relevant art.

Therefore, withdrawal of the § 112(1) rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claims 1-2, 4-7, 9-24, 43-44, 46, 48-50, and 61 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. (J. Clin. Invest., 105:1573 (2000)) in view of Kiyomiya et al. (Cancer Res., 61:2467 (2001)), Maitra et al. (Am. J. Physiol. Cell Physiol., 280:C1031 (2001)) and Englehardt (U.S. Patent No. 6,436,392). Claim 62 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Duan et al. in view of Kiyomiya et al., Maitra et al., and Englehardt, and 61, and in further view of Voinea et al. (J. Cell. Mol. Med., 6:465 (2002)). These rejections are respectfully traversed.

Duan et al. disclose that the combined effects of EGTA and LLnL on AAV transduction might be due to reduced degradation of internalized virus and an increased rate of endocytosis,

and that the combination enhanced the amount of virus internalized from apical surfaces (page 1583). As LLnL does not alter AAV binding to cell surfaces or internalization (page 1581), it is likely EGTA altered AAV binding to cell surfaces or internalization, i.e., EGTA is not an inhibitor of proteosome proteolytic activity. In addition, EGTA is not a chemotherapeutic, lipid lowering agent, antibiotic or tannic acid.

Kiyomiyo et al. disclose a mechanism for the nuclear transport of adriamycin, which may involve binding of adriamycin to the 20S proteosome. There is nothing in Kiyomiyo et al. related to virus transduction.

Maitra et al. relate that a single dose of doxorubicin increased total cellular CFTR protein expression, surface CFTR protein expression and CFTR-associated chloride secretion in T84 epithelial cells, and increased mutant CFTR cell surface expression and chloride secretion in stably transfected MDCK cells. Maitra et al. note that while the concentration of doxorubicin used *in vitro* (0.25 μ M) was about 20-fold lower than the LD₅₀, doxorubicin is unlikely to be useful in a clinical setting due to its cumulative systemic toxicity (page C1037). There is nothing in Maitra et al. related to virus transduction.

It is disclosed in the '392 patent that rAAV vectors, each containing a promoter and an open reading frame between ITRs, may become linked after infection of the host cell with the vectors and synthesis of double-stranded viral DNA (column 4, lines 41-56 and column 5, lines 26-38). Other vectors disclosed in the '392 patent include rAAV vectors that contain an open reading frame flanked by a splice site, i.e., one rAAV vector contains a splice acceptor site and another rAAV vector contains a splice donor site, which vectors together encode a functional gene product (column 4, lines 57-column 5, line 25). It is disclosed that transcription of a molecule formed by linking the two rAAVs in a cell results in a spliced RNA molecule which encodes a functional peptide (column 49, lines 14-22).

The '392 patent is not concerned with administering agents that enhance AAV transduction.

Voinea et al. disclose that liposome vesicles are useful drug delivery vehicles. It is disclosed that Doxil[®] is a suspension of doxorubicin precipitated in 80-100 nm sterically stabilized liposomes.

The Examiner asserts that, based on Duan et al., Kiyomiya et al., and Maitra et al., the administration of doxorubicin would be reasonably expected to achieve two therapeutic mechanisms in the treatment of cystic fibrosis, namely increased expression of CFTR to ameliorate the symptoms of the disease and enhance rAAV viral transduction because doxorubicin inhibits the proteasome protease. The Examiner continues asserting that it would have been obvious to one of ordinary skill in the art to try combining the proteasome inhibitor LLnL with doxorubicin with a reasonable chance of success because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.

There is no combination of the cited documents that discloses or suggests the use of the recited combination of agents and, given the disclosure of agents that likely interact with proteasomes in Duan et al. and Kiyomiya et al., it is unexpected that a combination of agents such as those with purportedly the same target would at least additively enhance AAV transduction, as those agents may be competitors for binding to the proteosome. Moreover, in the absence of Applicant's disclosure, there is nothing in the cited art that would provide one of skill in the art with a reason to select the recited agents to enhance AAV transduction (which unlike EGTA do not enhance AAV uptake at the cell membrane), particularly in view of Duan et al. which teach the use of an agent that alters AAV binding to cell surfaces or internalization and an agent that inhibits proteasome proteolytic activity or otherwise reduces degradation of internalized virus. Further, Maitra et al. teach away from the use of doxorubicin "in a clinical setting".

Accordingly, withdrawal of the § 103 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date

July 23, 2008

By

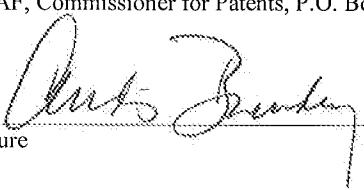
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 1: Biochem Soc Trans. 2003 Jun;31(Pt 3):487-92.

Transactions

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Antibiotic glycosyltransferases.

Walsh CT, Losey HC, Freel Meyers CL.

Department of Biological Chemistry & Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA. christopher_walsh@hms.harvard.edu

In the biosynthesis of several classes of antibiotics, sugars are attached to aglycone scaffolds by antibiotic-specific glycosyltransferases in the latter stages of the pathways. Two glycosylation pathways will be examined: the glycopeptide antibiotics of the vancomycin class and the aminocoumarin antibiotics of the novobiocin class. An oxidatively cross-linked heptapeptide scaffold is sequentially glucosylated and vancosaminylated by GtfE and GtfD, respectively, in vancomycin maturation, while in chloroeremomycin assembly the same heptapeptide is glucosylated by GtfB, then epivancosaminylated at two distinct sites by GtfA and GtfC. The specificity and mechanism of these glycosyltransferases will be discussed. In novobiocin biosynthesis, three enzymes (NovM, NovP and NovN) are thought to act sequentially to transfer an L-noviose moiety to the novobiocin acid aglycone (NovM), followed by 4'-hydroxyl methylation (NovP) and 3'-hydroxyl carbamoylation to produce the mature antibiotic structure, targeting the GyrB subunit of DNA gyrase. Initial characterization of NovM and NovP will be discussed.

PMID: 12773141 [PubMed - indexed for MEDLINE]

Related Articles

Structure of the UDP-glucosyltransferase GtfB that modifies the heptapeptide aglycone in the biosynthesis of vancomycin group antibiotics. [Structure. 2001]

Initial characterization of novobiocin acid noviosyl transferase activity of NovM in biosynthesis of the antibiotic novobiocin. [Biochemistry. 2003]

Tandem action of glycosyltransferases in the maturation of vancomycin and teicoplanin aglycones: novel glycopeptides. [Biochemistry. 2001]

A systematic investigation of the synthetic utility of glycopeptide glycosyltransferases. [Am Chem Soc. 2005]

Characterization of a regiospecific epivancosaminyl transferase GtfA and enzymatic reconstitution of the antibiotic chloroeremomycin. [Proc Natl Acad Sci U S A. 2004]

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1: Curr Opin Investig Drugs, 2002 Dec;3(12):1701-11.

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Antibacterial agents: patent highlights January to June 2002.

Phillips OA, Matowe WC.

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Kuwait University, PO Box 24923, Safat 13110, Kuwait. dphillips@hsc.kuniv.edu.kw

A total of 48 patents dealing with disclosures on the different classes of antibacterial agents, including the beta-lactams, oxazolidinones, macrolides, quinolones, tetracyclines and miscellaneous antibacterial agents reported between January and June 2002 are selected for review. The miscellaneous agents section focused on the significant discovery of potential lead compounds as inhibitors of bacterial fatty acid synthase and peptide deformylase, and also included examples of novel peptidic antibiotics and pleuromutilin derivatives along with their antibacterial activities. Only a few patents disclosed novel agents in the quinolone and carbapenem areas. There are several patents disclosing improved formulation of old agents to increase their effectiveness and stability upon storage. Two patents disclosed effectiveness of antibiotic combinations with respect to the newer antibiotics linezolid and quinupristin/dalfopristin.

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Antibacterial agents: patent highlights January to June 2004. [Curr Opin Investig Drugs. 2004]

Antibacterial agents: patent highlights January to June 2003. [Curr Opin Investig Drugs. 2003]

Antibacterial agents: patent highlights January 2005 to June 2005. [Curr Opin Investig Drugs. 2005]

Antibacterial agents (oxazolidinones, quinolones, macrolides and new agents): patent highlights June to December 2000. [Curr Opin Investig Drugs. 2001]

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Linezolid (Zyvox®) Linezolid is used to treat infections, including pneumonia, urinary tract infections, and infections of the skin and blood. Linezolid is in a class of antibiotics called oxazolidinones. It works by stopping the growth...

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1: Curr Med Chem. 2002 Sep;9(18):1655-65.

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Acridine derivatives as chemotherapeutic agents.

Denny WA.

Auckland Cancer Society Research Centre, Faculty of Medical and Health Sciences, The University of Auckland, Auckland, Private Bag 92019, New Zealand.
b.denny@auckland.ac.nz

Acridine derivatives are one of the oldest classes of bioactives, widely used as antibacterial and antiprotozoal agents. Some work in these areas continues, but recent research has focused mainly on their use as anticancer drugs, because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase enzymes.

PMID: 12171548 [PubMed - indexed for MEDLINE]

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The search of DNA-intercalators as antitumoral drugs: what it worked and what did not [Curr Med Chem. 2005]

DNA-binding antitumor agents: from pyrimido[5,6,1-de]acridines to other intriguing classes of acridine derivatives. [Curr Med Chem. 2002]

[The structural and functional analysis of the biological activity of acridine derivatives] [Akad Med Nauk. 2004]

Influence of polyamine architecture on the transport and topoisomerase II inhibitory properties of polyamine DNA-intercalator conjugates. [J Med Chem. 2001]

Design, synthesis, and biological properties of new bis (acridine-4-carboxamides) as anticancer agents [Anticancer Res. 2003]

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BIOSCIENCE
Open Access**Classical chemotherapy: mechanisms, toxicities and the therapeutic window.****Malhotra V, Perry MC.**Division of Hematology/Medical Oncology, University of Missouri-Ellis Fischel Cancer Center, Columbia, Missouri 65203 USA. malhotrav@health.missouri.edu

Chemotherapy can be best used by understanding the principles of pharmacology, tumor biology, cellular kinetics and drug resistance. Here we try to focus on the major classes of chemotherapeutic drugs, their mechanisms of action, toxicities; and the therapeutic window.

PMID: 14508075 [PubMed - indexed for MEDLINE]

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Mechanisms of cellular resistance to camptothecins. [Cancer Chemother Pharmacol. 2006]

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 1: Ann Pharmacother. 2005 Mar;39(3):523-6. Epub 2005 Jan 25. Full Text
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Effect of lipid-lowering drug therapy on small-dense low-density lipoprotein.**Backes JM, Gibson CA.**

Department of Pharmacy Practice, School of Pharmacy, University of Kansas Medical Center, 3901 Rainbow Boulevard, Kansas City, KS 66160-7231, USA. jbackes@kumc.edu

OBJECTIVE: To review the effects of lipid-lowering therapy on small-dense low-density lipoprotein cholesterol (sdLDL-C). **DATA SOURCES:** Literature was obtained from MEDLINE (1989-September 2004) and references of selected articles. Key search terms included small-dense LDL-C and lipid-lowering drug therapy. **DATA SYNTHESIS:** Statins, fibrates, and niacin have demonstrated favorable effects on sdLDL-C, especially among patients with mixed dyslipidemia or hypertriglyceridemia. These effects include a reduction of sdLDL-C and/or a shift to the larger, less atherogenic LDL-C. **CONCLUSIONS:** Data suggest that statins, fibrates, and niacin are effective at reducing concentrations of sdLDL-C and possibly normalizing LDL-C subclasses.

PMID: 15671087 [PubMed - indexed for MEDLINE]

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Optimal management of combined dyslipidemia: what have we learned from statins monotherapy? [J Am Cardiol. 2008]

Beyond low-density lipoprotein: addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome [Am J Cardiov Drugs. 2005]

Niacin as a component of combination therapy for dyslipidemia. [Mayo Clin Proc. 2003]

Niacin-ER and lovastatin treatment of hypercholesterolemia and mixed dyslipidemia. [J Am Cardiol. 2003]

Treatment of dyslipidaemias in patients with established vascular disease [Cerebrovasc Dis. 2000]

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Niacin (Advicor®, Niacor®, Niaspan®). Niacin is used with diet changes (restriction of cholesterol and fat intake) to reduce the amount of cholesterol and certain fatty substances in your blood. Niacin is also used to prevent and treat pellagra (niacin defic...

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 1: Prog Cardiovasc Dis. 2004 Sep-Oct;47(2):73-104.

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Comparative effects of lipid-lowering therapies.

Davidson MH, Toth PP.

Radiant Research, Rush Medical College, Rush University Medical Center, Chicago, IL 60602, USA. michaeldavidson@radiantrresearch.com

The pharmacologic regulation of lipid metabolism in patients with dyslipidemia is unequivocally associated with significant reductions in risk for cardiovascular morbidity and mortality. A number of therapeutic drug classes have been developed in an effort to ever more precisely and intensively modulate lipid metabolism. Statins, fibrates, ezetimibe, and niacin exert their effects via different mechanisms and afford physicians the opportunity to beneficially impact multiple pathways in patients. When used alone or in combination, these drugs decrease risk for the development and progression of atherosclerotic disease. There are strong clinical trial data to support the use of lipid-lowering therapies in the settings of both primary and secondary prevention. This article (1) discusses the mechanisms of action of antilipidemic medications, (2) reviews dosing regimens and the pharmacokinetic differences among drugs of the same class, (3) assesses risk for drug interactions, and (4) reviews the clinical trial evidence used to support the use of particular antilipidemic medications in specific physiologic settings. The incidence of dyslipidemia is rising worldwide. This trend portends an ever-growing need for the aggressive and judicious use of different antilipidemic medication(s) in patients at risk for all forms of atherosclerotic vascular disease.

PMID: 15586350 [PubMed - indexed for MEDLINE]

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Lipid-lowering effects of statins: a comparative review.
[Expert Opin Pharmacother. 2006]High-density lipoprotein metabolism: potential therapeutic targets.
[Am J Cardiol. 2007]

Lipid lowering effects of statins and fibrates in the management of HIV dyslipidemias associated with antiretroviral therapy in HIV clinical practice. [J Acquir Immune Defic Syndr. 2004]

The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy. [Clin Ther. 2004]

Lipid-lowering drugs.
[Cell Mol Life Sci. 2006]

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Niacin (Advicor®, Niacor®, Niaspan®). Niacin is used with diet changes (restriction of cholesterol and fat intake) to reduce the amount of cholesterol and certain fatty substances in your blood. Niacin is also used to prevent and treat pellagra (niacin defic...

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Ezetimibe (Vytorin® (as a combination product containing Ezetimibe and Simvastatin), Zetia®)

Ezetimibe is used together with lifestyle changes (diet, weight-loss, exercise) to reduce the amount of cholesterol (a fat-like substance) and other fatty substances in the blood. It may be used alone or in combination w...

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1: Crit Rev Food Sci Nutr. 1998 Aug;38(6):421-64.

Links

Tannins and human health: a review.

Chung KT, Wong TY, Wei CI, Huang YW, Lin Y.

Department of Microbiology and Molecular Cell Sciences, University of Memphis, TN 38152, USA.

Tannins (commonly referred to as tannic acid) are water-soluble polyphenols that are present in many plant foods. They have been reported to be responsible for decreases in feed intake, growth rate, feed efficiency, net metabolizable energy, and protein digestibility in experimental animals. Therefore, foods rich in tannins are considered to be of low nutritional value. However, recent findings indicate that the major effect of tannins was not due to their inhibition on food consumption or digestion but rather the decreased efficiency in converting the absorbed nutrients to new body substances. Incidences of certain cancers, such as esophageal cancer, have been reported to be related to consumption of tannins-rich foods such as betel nuts and herbal teas, suggesting that tannins might be carcinogenic. However, other reports indicated that the carcinogenic activity of tannins might be related to components associated with tannins rather than tannins themselves. Interestingly, many reports indicated negative association between tea consumption and incidences of cancers. Tea polyphenols and many tannin components were suggested to be anticarcinogenic. Many tannin molecules have also been shown to reduce the mutagenic activity of a number of mutagens. Many carcinogens and/or mutagens produce oxygen-free radicals for interaction with cellular macromolecules. The anticarcinogenic and antimutagenic potentials of tannins may be related to their antioxidative property, which is important in protecting cellular oxidative damage, including lipid peroxidation. The generation of superoxide radicals was reported to be inhibited by tannins and related compounds. The antimicrobial activities of tannins are well documented. The growth of many fungi, yeasts, bacteria, and viruses was inhibited by tannins. We have also found that tannic acid and propyl gallate, but not gallic acid, were inhibitory to foodborne bacteria, aquatic bacteria, and off-flavor-producing microorganisms. Their antimicrobial properties seemed to be associated with the hydrolysis of ester linkage between gallic acid and polyols hydrolyzed after ripening of many edible fruits. Tannins in these fruits thus serve as a natural defense mechanism against microbial infections. The antimicrobial property of tannic acid can also be used in food processing to increase the shelf-life of certain foods, such as catfish fillets. Tannins have also been reported to exert other physiological effects, such as to accelerate blood clotting, reduce blood pressure, decrease the serum lipid level, produce liver necrosis, and modulate immunoresponses. The dosage and kind of tannins are critical to these effects. The aim of this review is to summarize and analyze the vast and sometimes conflicting literature on tannins and to provide as accurately as possible the needed information for assessment of the overall effects of tannins on human health.

PMID: 9759559 [PubMed - indexed for MEDLINE]

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Lycopene in tomatoes: chemical and physical properties affected by food processing. [\[Crit Rev Food Sci Nutr. 2000\]](#)

Cooperation of liver cells in health and disease. [\[Adv Anat Embryol Cell Biol. 2001\]](#)

Final report on the safety assessment of capsicum annuum extract, capsicum annuum fruit extract, capsicum annuum resin, capsicum annuum fruit powder, capsicum frutescens fruit, capsicum frutescens fruit extract, capsicum frutescens resin, and capsaicin. [\[Int J Toxicol. 2007\]](#)

Nutritional toxicology of tannins and related polyphenols in forage legumes. [\[J Anim Sci. 1995\]](#)

Upflow anaerobic sludge blanket reactor-a review. [\[Indian J Environ Health. 2001\]](#)

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0006662982 **CAB Accession Number:** 19930103065

Use of Adeno-associated virus as a general transduction vector for mammalian cells.

Muzyczka, N.
Department of Microbiology, SUNY Stony Brook Medical School, Stony Brook, NY
11794, USA.
Current Topics in Microbiology and Immunology vol. 158 p.97-129
Publication Year: 1992
ISSN: 0070-217X
Language: English **Record Type:** Abstract

Document Type: Journal article

A review. Adeno-associated virus (AAV) is a human virus that can be propagated either as an integrated provirus or by lytic infection. AAV usually requires the presence of a helper virus, for example a herpes or adenovirus, to initiate a productive viral infection. In the absence of a helper virus, AAV integrates into a host chromosome. A peculiar feature of AAV which makes it attractive as a mammalian transduction vector is that if a cell carrying an AAV provirus is subsequently superinfected with a helper virus, the AAV genome is excised and proceeds through a normal productive infection cycle. This review focuses on the progress towards producing AAV vectors. The suitability of such vectors for human gene therapy is discussed. 155 ref.

Descriptors: Biotechnology; gene expression; reviews; Vectors

Organism Descriptors: Adeno-associated virus

Broader Terms: Parvoviridae; ssDNA viruses; DNA viruses; viruses

CABI Codes: Biotechnology (General), (Revised June 2002) (WW000); Parasites, Vectors, Pathogens and Biogenic Diseases of Animals, (Discontinued March 2000) (LL820)

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 1: *Antimicrob Agents Chemother*. 2004 Jul;48(7):2437-47.Final Version **FREE**
aac.asm.orgFull text article
in PubMed Central**Model system for high-throughput screening of novel human immunodeficiency virus protease inhibitors in *Escherichia coli*.****Cheng TJ, Brik A, Wong CH, Kan CC.**

Keck Graduate Institute of Applied Life Sciences, 535 Watson Drive, Claremont, CA 91711, USA.

Novel human immunodeficiency virus (HIV) protease inhibitors are urgently needed for combating the drug-resistance problem in the fight against AIDS. To facilitate lead discovery of HIV protease inhibitors, we have developed a safe, convenient, and cost-effective *Escherichia coli*-based assay system. This *E. coli*-based system involves coexpression of an engineered beta-galactosidase as an HIV protease substrate and the HIV protease precursor comprising the transframe region and the protease domain. Autoprocessing of the HIV protease precursor releases the mature HIV protease. Subsequently, the HIV protease cleaves beta-galactosidase, resulting in a loss of the beta-galactosidase activity, which can be detected in high-throughput screens. Using Food and Drug Administration-approved HIV protease inhibitors, this *E. coli*-based system is validated as a surrogate screening system for identifying inhibitors that not only possess inhibitory activity against HIV protease but also have solubility and permeability for *in vivo* activity. The usefulness of the *E. coli*-based system was demonstrated with the identification of a novel HIV protease inhibitor from a library of compounds that were prepared by an amide-forming reaction with transition-state analog cores. A novel inhibitor with a sulfonamide core of amprenavir, E2, has shown good correlation with the *in vitro* enzymatic assay and *in vivo* *E. coli*-based system. This system can also be used to generate drug resistance profiles that could be used to suggest therapeutic uses of HIV protease inhibitors to treat the drug-resistant HIV strains. This simple yet efficient *E. coli* system not only represents a screening platform for high-throughput identification of leads targeting the HIV proteases but also can be adapted to all other classes of proteases.

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PMCID: PMC434161

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An *Escherichia coli* expression assay and screen for human immunodeficiency virus protease variants with decreased susceptibility to protease inhibitors. [Antimicrob Agents Chemother. 1998]

Toward the development of a virus-cell-based assay for the discovery of novel compounds against human immunodeficiency virus. [Antimicrob Agents Chemother. 2003]

A quick diversity-oriented amide-forming reaction to optimize P-subsites residues of HIV protease inhibitors. [Antimicrob Agents Chemother. 2003]

Peptides derived from HIV-1 Vif: a non-substrate based novel type of HIV-1 protease inhibitor. [Antimicrob Agents Chemother. 1999]

Screening for HIV protease inhibitors by protection against activily-mediated cytotoxicity in *Escherichia coli*. [J Virol Methods. 2006]

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Patient Drug Information

Amprenavir (Agenerase®): Amprenavir is used in combination with other antiretroviral medications to treat human immunodeficiency virus (HIV). Amprenavir belongs to a class of drugs called protease inhibitors, which slow the spread of HIV infection.

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 1: J Biol Chem. 2002 Oct 11;277(41):38322-7. Epub 2002 Aug 6.Final Version **FREE** J Biol Chem

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Identification and biological characterization of heterocyclic inhibitors of the hepatitis C virus RNA-dependent RNA polymerase.

Dhanak D, Duffy KJ, Johnston VK, Lin-Goerke J, Darcy M, Shaw AN, Gu B, Silverman C, Gates AT, Nonnemacher MR, Earnshaw DL, Casper DJ, Kaura A, Baker A, Greenwood C, Gutshall LL, Maley D, DelVecchio A, Macarron R, Hofmann GA, Alnoah Z, Cheng HY, Chan G, Khandekar S, Keenan RM, Sarisky RT.

Department of Medicinal Chemistry, The Musculoskeletal, Microbial and Proliferative Diseases Center of Excellence for Drug Discovery, GlaxoSmithKline Pharmaceuticals, Collegeville, Pennsylvania 19426, USA.

The hepatitis C virus (HCV) NS5B protein encodes an RNA-dependent RNA polymerase (RdRp), the primary catalytic enzyme of the HCV replicase complex. We established a biochemical RNA synthesis assay, using purified recombinant NS5B lacking the C-terminal 21 amino acid residues, to identify potential polymerase inhibitors from a high throughput screen of the GlaxoSmithKline proprietary compound collection. The benzo-1,2,4-thiadiazine compound 1 was found to be a potent, highly specific inhibitor of NS5B. This agent interacts directly with the viral polymerase and inhibits RNA synthesis in a manner noncompetitive with respect to GTP. Furthermore, in the absence of an *in vitro*-reconstituted HCV replicase assay employing viral and host proteins, the ability of compound 1 to inhibit NS5B-directed viral RNA replication was determined using the Huh7 cell-based HCV replicon system. Compound 1 reduced viral RNA in replicon cells with an IC₅₀ of approximately 0.5 microm, suggesting that the inhibitor was able to access the perinuclear membrane and inhibit the polymerase activity in the context of a replicase complex. Preliminary structure-activity studies on compound 1 led to the identification of a modified inhibitor, compound 4, showing an improvement in both biochemical and cell-based potency. Lastly, data are presented suggesting that these compounds interfere with the formation of negative and positive strand progeny RNA by a similar mode of action. Investigations are ongoing to assess the potential utility of such agents in the treatment of chronic HCV disease.

PMID: 12167642 [PubMed - indexed for MEDLINE]

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Resistance profile of a hepatitis C virus RNA-dependent RNA polymerase against thiadiazine and thiazine.

Specific inhibitors of HCV polymerase identified using an NS5B with lower affinity for template/primer substrate. [Nucleic Acids Res. 2004]

Arresting initiation of hepatitis C virus RNA synthesis using heterocyclic derivatives. [J Biol Chem. 2003]

Inhibition of native hepatitis C virus replicase by nucleotide and non-nucleoside inhibitor. [Virology. 2005]

Mutations in NS5B polymerase of hepatitis C virus: impacts on *in vitro* enzymatic activity and viral RNA replication in the subgenomic replicon. [Virology. 2002]

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 1: Vision Res. 2008 Jul;48(15):1648-1654. Epub 2008 May 29.

ELSEVIER Links

Enhanced transduction and improved photoreceptor survival of retinal degeneration by the combinatorial use of rAAV2 with a lower dose of adenovirus.**Wu J, Zhang S, Wu X, Dong X, Xu P, Liu X, Li C, Huang Q.**

Experimental Research Center, EYE & ENT Hospital of Fudan University, 83 Fenyang Road, Shanghai 200031, China; Experimental Research Center, No. 1 People's Hospital, Shanghai Jiaotong University, 85 Wujin Road, Shanghai 200080, China.

Recombinant adeno-associated virus (rAAV) is widely used in retinal gene therapy. Enhanced rAAV transduction may be important for better therapeutic effects in some retinal gene therapies. In this study, we examined the effects of adenovirus 5 (Ad5) on retina transduction mediated by rAAV2. Our results provide the first evidence that low levels of either replication-incompetent or conditional replication-competent Ad5 significantly enhance and accelerate transgene expression in human and rat retinal cells. This effect occurs principally at the transcriptional level, rather than through enhanced viral entry or DNA replication. In *in vivo* analyses with the SD rat, the Balb/c mouse, and the RCS rat, strong enhancement and acceleration of transgene expression, as well as therapeutic effects, were confirmed. Low levels of Ad5 may enhance the utility of rAAV2-mediated transduction strategies in future clinical investigations.

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A histone deacetylase inhibitor enhances recombinant adeno-associated virus-mediated gene expression in tumor cells. [Mol Ther. 2006]

The recombinant adeno-associated virus vector (rAAV2)-mediated apolipoprotein B mRNA-specific hammerhead ribozyme: a self-complementary AAV2 vector improves the gene expression. [Antivir Ther. 2004]

Practical considerations of recombinant adeno-associated virus-mediated gene transfer for treatment of retinal degenerations. [J Gene Med. 2003]

Transduction efficacy of recombinant type 1 and type 2 adeno-associated virus in the retina. [Zhi. 2006]

Evaluation of recombinant adeno-associated virus as a gene transfer vector for the retina. [Curr Eye Res. 1997]

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1: Pathol Oncol Res. 2008 May 29. [Epub ahead of print]

**Effect of Small Interference RNA Targeting HIF-1alpha Mediated by rAAV Combined L: -Ascorbate on Pancreatic Tumors in Athymic Mice.****Chen C, Sun J, Liu G, Chen J.**

Department of Surgery, The Second Hospital of TianJin Medical University, Tianjin, 300211, China.

To study the effect of recombinant adeno-associated virus (rAAV) vector bearing small interference RNA (siRNA) targeting hypoxia inducible factor 1alpha (HIF-1alpha) combined L: -ascorbate on pancreatic tumors in athymic mice primarily. A cassette encoding siRNA targeting HIF-1alpha mediated by rAAV was constructed, giving rAAV-siHIF. In vitro, rAAV-hrGFP, rAAV-siHIF and L: -ascorbate which were used alone or in combination were delivered to exponentially growing MiaPaCa2 cells. Then, we examined the expression of HIF-1alpha mRNA and protein, the secretion of VEGF in MiaPaCa2 cells under hypoxic condition with Real-time PCR, Western Blot, ELISA, respectively. In vivo, MiaPaCa2 cells were inoculated subcutaneously on the back of nude mice. Nude mice with xenograft tumor were randomly divided into equal groups and were injected with rAAV-hrGFP or rAAV-siHIF or were fed with L: -ascorbate. Then, we measured the size of tumor every 3 days and drew a tumor growth curve. After 30 days, all mice were sacrificed and the tumors were dissected. At last, we examined the expression of HIF-1alpha, VEGF and CD34 by immunohistochemistry and counted micro-vessel density (MVD). In vitro, we found that rAAV-siHIF could inhibit the expression of HIF-1alpha mRNA and protein in MiaPaCa2 human pancreatic cancer cells but L: -ascorbate could only restrain the expression of HIF-1alpha protein. Moreover, rAAV-siHIF and L: -ascorbate could all inhibit the secretion of vascular VEGF. In vivo, we found that rAAV-siHIF could inhibit the growth of nude mice xenograft tumor and the expression of HIF-1alpha and VEGF and MVD while L: -ascorbate can only inhibit the growth of xenograft tumor in the early and middle stage. These results suggest that rAAV-siHIF and L: -ascorbate can inhibit the growth of nude mice xenograft tumor and HIF-1alpha could be a target of pancreatic cancer genetic and pharmacological therapy.

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Hypoxia inducible factor-1 mediates effects of insulin on pancreatic cancer cells and disturbs host energy homeostasis. *[Am J Pathol. 2007]*

Inhibition of hypoxia inducible factor-1alpha (HIF-1alpha) decreases vascular endothelial growth factor (VEGF) secretion and tumor growth in malignant gliomas. *[J Neurooncol. 2006]*

The transcriptional activator hypoxia inducible factor 2 (HIF-2/EPAS-1) regulates the oxygen-dependent expression of erythropoietin in cortical astrocytes. *[J Neurooncol. 2006]*

Role of hypoxia-inducible factor 1alpha in gastric cancer cell growth, angiogenesis, and vessel maturation. *[J Natl Cancer Inst. 2004]*

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1: Pharm Res. 2008 Feb 22. [Epub ahead of print]

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Glucose- and Metabolically Regulated Hepatic Insulin Gene Therapy for Diabetes.

Hsu PY, Kotin RM, Yang YW.

School of Pharmacy, College of Medicine, National Taiwan University, 1, Jen-Ai Road, Section 1, Taipei, 100, Taiwan.

PURPOSE: The purpose of this study was to examine glucose- and metabolically modulation of insulin secretion by rAAV-mediated gene delivery in vitro and in vivo. **MATERIALS AND METHODS:** A recombinant adeno-associated virus vector (rAAV) containing a furin-mutated human insulin gene, driven by the rat insulin I promoter, was used in this study. Glucose-responsive secretion of human insulin was determined by treating rAAV-transduced Huh7 human hepatoma cells with varying concentrations of glucose, with or without insulin secretagogues. Glucose- and metabolically modulated secretion of human insulin in the streptozotocin (STZ)-induced diabetic mice was assessed by intrahepatic administration of rAAV-polyethylenimine (PEI) complexes, followed by intraperitoneal glucose tolerance test (IPGTT), with or without theophylline. **RESULTS:** Glucose- and metabolically controlled human insulin secretion was obtained in the rAAV-transduced Huh7 cells. Treatment of STZ-induced diabetic animals with rAAV-polyethylenimine (rAAV-PEI) complexes resulted in production of human insulin and amelioration of hyperglycemia. Co-administration of glucose and theophylline in these animals augmented the secretion of human insulin, demonstrating metabolic modulation of insulin secretion in vivo. Immunohistochemical examination of the liver sections of rAAV-treated mice confirmed the production of human insulin. **CONCLUSIONS:** Glucose- and metabolically controlled hepatic insulin gene therapy was obtained both in vitro and in vivo.

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Effect of polyethylenimine on recombinant adeno-associated virus mediated insulin gene therapy [J Gene Med. 2005]

Incorporation of calcium phosphate enhances recombinant adeno-associated virus-mediated gene therapy in diabetic mice. [J Gene Med. 2003]

Glucose-modulated transgene expression via recombinant adeno-associated virus [Pharm Res. 2002]

Safety and efficacy of adeno-associated viral vector-mediated insulin gene transfer via portal vein to the livers of streptozotocin-induced diabetic Sprague-Dawley rats. [J Gene Med. 2005]

Glucose transporter-2 (GLUT2) promoter mediated transgenic insulin production reduces hyperglycemia in diabetic mice. [FEBS Lett. 2005]

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Theophylline (Bronkodyl®, Elixophyllin®, Slo-bid®, ...) Theophylline is used to prevent and treat wheezing, shortness of breath, and difficulty breathing caused by asthma, chronic bronchitis, emphysema, and other lung diseases. It relaxes and opens air passages in the lungs, ...

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